

PB88-129598

Health and Environmental Effects Profile for
Benzenamine, 4, 4'-Methylenebis

(U.S.) Environmental Protection Agency
Cincinnati, OH

Jan 84



U.S. Department of Commerce
National Technical Information Service
NTIS

EPA/600/X-84/231
January 1984

HEALTH AND ENVIRONMENTAL EFFECTS PROFILE
FOR BENZENAMINE, 4,4'-METHYLENEBIS

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
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U.S. ENVIRONMENTAL PROTECTION AGENCY
CINCINNATI, OH 45268

TECHNICAL REPORT DATA
(Please read instructions on the reverse before completing)

1. REPORT NO. EPA/600/X-84/231		2. RECIPIENT'S ACCESSION NO.	
4. TITLE AND SUBTITLE Health and Environmental Effects Profile for Benzenamine, 4,4'-Methylenebis		5. REPORT DATE January 1984	
7. AUTHOR(S)		6. PERFORMING ORGANIZATION CODE	
9. PERFORMING ORGANIZATION NAME AND ADDRESS		8. PERFORMING ORGANIZATION REPORT NO.	
12. SPONSORING AGENCY NAME AND ADDRESS Environmental Criteria and Assessment Office Office of Research and Development U.S. Environmental Protection Agency Cincinnati, OH 45268		10. PROGRAM ELEMENT NO.	
		11. CONTRACT/GRANT NO.	
		13. TYPE OF REPORT AND PERIOD COVERED	
		14. SPONSORING AGENCY CODE EPA/600/22	
15. SUPPLEMENTARY NOTES			
16. ABSTRACT The Health and Environmental Effects Profile for <u>benzenamine, 4,4'-methylene bis</u> was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents. Quantitative estimates have been presented provided sufficient data are available. <u>Benzenamine, 4,4'-methylene bis</u> has been evaluated as a carcinogen. The human carcinogen potency factor (q₁*) for <u>benzenamine, 4,4'-methylene bis</u> is 2.5×10^{-2} (mg/kg bw/day)⁻¹ for oral exposure.			
17. KEY WORDS AND DOCUMENT ANALYSIS			
a. DESCRIPTORS		b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field Group
18. DISTRIBUTION STATEMENT Public		19. SECURITY CLASS (This Report) Unclassified	21. NO. OF PAGES 35
		20. SECURITY CLASS (This page) Unclassified	22. PRICE

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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste by the Office of Health and Environmental Assessment. The HEEP's are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include, Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor or q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEE's will become part of the EPA RCRA docket.

ACKNOWLEDGEMENTS

The initial draft of this report was prepared by Syracuse Research Corporation under Contract No. 68-03-3228 for U.S. EPA's Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH. Dr. Christopher DeRosa was the Technical Project Monitor and Helen Ball was the Project Officer. The final documents in this series were prepared for the Office of Solid Waste, Washington, DC.

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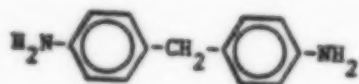
LIST OF ABBREVIATIONS

bw	Body weight
DNA	Deoxyribonucleic acid
ppm	Parts per million
STEL	Short-term exposure limit
TLV	Threshold limit value

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

4,4'-Methylenebisbenzenamine is known by a number of names, the most common of which include the following: 4,4'-methylenedianiline (MDA); 4,4'-diaminodiphenyl methane; methylenedianiline; and p,p'-methylenedianiline. Throughout this profile it will be referred to as MDA. This chemical has been produced for ~50 years (IARC, 1974). The structure of MDA is depicted below:



Molecular formula: $C_{13}H_{14}N_2$

Molecular weight: 198.26

The Chemical Abstracts Service (CAS) Registry Number for this compound is 101-77-9.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

MDA is a pale yellow crystal that darkens when exposed to air (IARC, 1974). It is slightly soluble in water and is soluble in alcohol, benzene, ether and many other organic solvents (Moore, 1978). Some of the physical properties are listed below:

Melting point:	93°C (IARC, 1974)
Boiling point:	398-399°C at 768 mm Hg (Weast, 1980)
Log octanol/water partition coefficient:	1.59 (Hansch and Leo, 1981) 1.76-2.52 (Newman et al., 1981)
Vapor pressure:	10 mm Hg at 25°C (Dorigan et al., 1976)
Partition coefficient in soil standardized with respect to soil organic carbon content (K_{oc}):	1.79-2.62 (Newman et al., 1981)

Solubility: 1 g/kg in water at 25°C (Moore, 1978)
Liquid density
at 100°C compared
to water at 4°C 1.056 g/cm³ (Moore, 1978)
Heat of vaporization: 22.8 kcal/mole (Moore, 1978)

1.3. PRODUCTION DATA

Commercially, MDA is prepared by the reaction of formaldehyde with aniline, which produces a mixture of di-, tri- and polyamines from which the diamine can be isolated. Only a small amount of MDA is isolated from the mixture, which is usually converted directly to polyisocyanates (specifically "polymeric" methylene diphenyl) by the reaction with phosgene. MDA can also be made in the laboratory by the hydrogenolysis reaction of p,p'-diaminobenzophenone with lithium aluminum hydride (IARC, 1974). The domestic producers of MDA are listed below (SRI, 1983):

E.I. du Pont de Nemours and Co., Inc.
ICI Americas Inc.
Olin Corp.
Uniroyal, Inc.
The Upjohn Co.

Deepwater, NJ
Gelsmer, LA
Moundsville, WV
Naugatuck, CT
La Porte, TX

According to an EPA notice published in the Federal Register (1983), ~200-400 million pounds of MDA is produced annually in the United States.

1.4. USE DATA

Approximately 90% of the annual production of MDA is used captively in the manufacture of methylenediphenyl diisocyanate (MDI), which is used to manufacture polyurethane foams. About 9% of the total MDA is transferred to other locations for MDI production. The remaining MDA is used in the manufacture of specialty products such as the following as: epoxy resins; a corrosion preventative for iron; an antioxidant for lubricating oils; a rubber processing chemical; in the manufacture of 4,4'-methylenebis(cyclohexaneamine), which is in turn used in the manufacture of elastomeric fibers; and other miscellaneous uses (Federal Register, 1983; Moore, 1978).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

MDA may be released into the environment through air or water effluent from manufacturing or user plants and from MDI manufacturing plants. According to a U.S. EPA notice published in 1983 in the Federal Register, however, there are no data that document MDA's presence in the environment, and if any release occurs it is predicted to be low (Federal Register, 1983).

Pertinent data regarding the fate and transport of this chemical in the atmosphere were not located in the available literature.

Limited data were available on the fate and transport of this chemical in the aquatic media. Calculated values such as a log bioconcentration factor of 1-46 (Federal Register, 1983) and a log octanol/water partition coefficient of 1.59-2.52 (Hansch and Leo, 1981; Federal Register, 1983) suggest that uptake and subsequent concentration by aquatic organisms is unlikely. Although no specific studies were located regarding the persistence of MDA in the aquatic environment, some information was available in the Federal Register. Based on physical properties of MDA and estimates of equilibrium constants and second-order kinetic rates for structurally related compounds (toluene and aniline), maximum exposure levels of MDA under normal conditions are estimated to range from 10^{-1} to 10^{-4} mg/l in the water column of river systems receiving effluent from MDA manufacturing plants (Federal Register, 1983). The U.S. EPA's EXAMS modeling systems predict that MDA would persist in the water column and sediment of these river systems 0.2-6.5 days and that oxidation would have the greatest impact on MDA in the environment (Federal Register, 1983). Therefore, based on this information, it is unlikely that MDA would be present in high enough concentrations or would persist long enough to be of environmental concern.

According to the U.S. EPA, once MDA is converted into polyurethane materials there is very little likelihood that MDA will be released into the environment in significant amounts (Federal Register, 1983). Results of a study summarized in the Federal Register indicated that ^{14}C -labeled toluene diisocyanates were resistant to microbial degradation under sanitary landfill conditions (Federal Register, 1983). Based on these results, the U.S. EPA stated that little regeneration and release of MDA would be expected under landfill situations and any MDA released is expected to be degraded chemically or microbially as suggested by the occurrence of ^{14}C -labeled CO_2 in the toluene diisocyanate study (Federal Register, 1983). No other information regarding the fate or transport of this chemical in the soil was located in the available literature.

3. EXPOSURE

According to a U.S. EPA notice published in the Federal Register in 1983, human exposure to MDA appears to occur principally in the workplace as a result of uses other than MDI manufacture. NIOSH currently estimates that 12,000-13,000 people may be exposed to MDA in the workplace, and the Chemical Manufacturers Association (CMA) estimates that ~600 people are potentially exposed to MDA during the manufacture as an MDI intermediate (Federal Register, 1983). The Federal Register further stated that data from industrial monitoring studies indicate that airborne concentrations of MDA can be as high as 3.8 ppm during the transfer of molten MDA and during grinding and packaging operations. MDA levels have also been reported as low as 0.0064 ppm during these operations (Federal Register, 1983). Lewis (1980) reported that a survey conducted in 1979 at the Fisher and Porter Company revealed levels ranging from undetectable to 0.01 mg/m³ MDA in the work air.

The U.S. EPA concluded that except for data submitted in 1981 revealing the release of small quantities of MDA into unspecified environmental compartments, there are currently no data that show any release of MDA into the environment (Federal Register, 1983).

No monitoring data for MDA were available in STORET.

4. PHARMACOKINETICS

Pertinent data regarding the absorption, distribution, metabolism or excretion of MDA were not located in the available literature. It can be inferred, however, from animal toxicity studies and human case reports that gastric and dermal absorption of MDA occurs (Chapter 5).

5. EFFECTS

5.1. CARCINOGENICITY

Munn (1967) administered MDA in arachis oil by gavage to a group of 24 male rats near the maximum tolerated dose 5 days/week for 121 days. The total dose was 3.3 g/kg bw. Mortality and pathologies of the exposed rats were observed after treatment until their natural death. All animals developed hepatic cirrhosis. No tumors were found in 12 animals that died before 2 years, and two benign hepatomas and various other tumors (types not specified) were reported in animals surviving >2 years. The apparent lack of an appropriate control group precludes any conclusion regarding the significance of these data. In a similar experiment rats were dosed intragastrically for ~18 months (total dose ~6 g/kg) (Munn, 1967). Tumors of various sites (2 liver tumors, 2 subcutaneous fibromas, 1 intestinal tumor and 1 pituitary tumor) were reported. No controls were used for comparison.

Steinhoff and Grundmann (1970) intermittently treated 50 Wistar rats (25 of each sex) subcutaneously with MDA (30-50 mg/kg) so that the total dose over a 705-day period was 1.41 g/kg. Fifty percent of the rats treated with MDA died of cancer, while 26% of the vehicle controls (physiological saline) also developed cancer. Thirty-three malignant and 29 benign tumors were reported in treated rats, while 16 and 15, respectively, occurred in controls (25 rats of each sex). Four hepatomas were found in the treated rats. The average lifespan of the rats was not different between the groups.

Yoshimura (1981) reported that MDA administered in the diet at 1000 ppm (1.0 g/kg diet) to male rats for 8-40 weeks did not appear to be carcinogenic. Reversible bile-duct hyperplasia was noted. Administration of MDA in combination with 1,2-dimethylhydrazine reduced the colon carcinogenic activity of the latter chemical (Yoshimura, 1981). Fukushima et al. (1981)

reported that MDA administered to rats in the diet or drinking water after initiation with N-ethyl-N-hydroxy-ethylnitrosamine or N-butyl-N-(4-hydroxybutyl) nitrosamine was inhibitory to liver, kidney and bladder carcinogenesis.

A long-term carcinogenesis bioassay on 4,4'-methylenedianiline dihydrochloride (MDA-2HCl) has been conducted in Fischer 344 rats and B6C3F1 mice (NTP, 1983). Fifty males and 50 females of both species were treated with MDA-2HCl at 150 or 300 mg MDA/l in the drinking water for 103 weeks. Control groups received pH-adjusted (3.7) drinking water. In rats, water consumption was slightly reduced in treated groups, but mean bw and survival were not different from controls, except for a decrease in bw in high-dose females. Following histopathological examination the incidence of hepatic neoplastic nodules was significantly elevated in low- (12/50; $P=0.001$ by Fisher Exact Test) and high- (25/50; $P<0.001$) dose male rats compared with controls (1/50). In high-dose male rats the incidence of thyroid follicular-cell carcinoma (7/48) was significantly ($P=0.006$) elevated above controls (0/49). Female rats treated at 300 mg MDA/l had significantly increased incidences of thyroid follicular-cell adenomas (17/48; $P<0.001$) and thyroid C-cell adenomas (6/48; $P=0.014$) compared with controls (0/47 for both tumor types).

Mice of both sexes treated at the high dose (300 mg MDA/l) had lower mean bw than controls and survival in high-dose males was also reduced (NTP, 1983). In high-dose males the incidence of thyroid follicular-cell adenoma (16/49; $P<0.001$), adrenal pheochromocytoma (14/49; $P=0.001$), and hepatocellular carcinoma (29/50; $P<0.001$) was significantly elevated compared with controls (0/47, 2/48 and 10/49, respectively). Hepatocellular carcinoma (33/50; $P<0.001$) and adrenal pheochromocytoma (12/49; $P<0.004$) were also

significantly elevated in low-dose (150 mg MDA/l) male mice. The incidence of thyroid follicular cell adenoma (13/50; $P < 0.001$), hepatocellular adenoma and carcinoma (23/50; $P < 0.001$), and malignant lymphoma (29/50; $P = 0.001$) was elevated in high-dose female mice compared with controls (0/50, 4/50 and 13/50, respectively). In low-dose females, hepatocellular adenoma and carcinoma (15/50; $P = 0.005$) and malignant lymphoma (28/50; $P = 0.002$) were also significantly elevated in a dose-related manner. Alveolar and bronchiolar adenoma and carcinoma were decreased in high-dose male mice (4/49 vs. 13/49 in controls; $P = 0.015$), but the same tumor types were significantly ($P = 0.043$) increased in high-dose female mice (8/49 vs. 2/50 in controls; $P = 0.043$).

Several tumor types with a very low incidence among historical controls were noted during this bioassay and include transitional-cell papillomas of the urinary bladder in female rats (2/50, 1/50 and 3/3644 in low-dose, high-dose and historical controls, respectively), ovarian granulosa cell tumors in rats (3/50, 2/50, 11/3642 in low-dose, high-dose and historical controls), and bile duct adenoma in high-dose male rats (1/50 vs. 0/3633 in historical controls, respectively). Statistical tests were not performed on these tumor types because of the low incidences, but their existence was regarded as possibly important. This bioassay concluded that MDA-2HC1 was carcinogenic in both sexes of rats and mice of the strains tested (NTP, 1983).

Deichmann et al. (1978) investigated the carcinogenicity of purified and crude MDA, which was administered orally at 70 mg/day (in corn oil in gelatin capsules) 3 days/week to the urinary bladders of female beagle dogs. No neoplastic changes were seen in the urinary bladders of the 5 dogs that received purified MDA and the 4 dogs that received crude MDA. There were no concurrent controls.

5.2. MUTAGENICITY

Lavoie et al. (1979) reported dose-related increases in histidine revertants in both TA100 and TA98 strains of Salmonella typhimurium in the presence of a rat-liver activation system (plate incorporation assay, 25-500 μ g MDA/plate). Revertants were more numerous in TA100 than in TA98 when compared with their respective controls. Only a slight increase in the number of revertants was reported in TA100 in the absence of an activation system. Rao et al. (1982) reported that MDA was mutagenic in tester strains TA98 and TA100 only when an activation system from phenobarbital or Aroclor-pretreated rats was available, but was not mutagenic to TA1535 or TA1537 strain in the presence or absence of an activation system (plate incorporation assay, dose not specified). Frameshift mutagenic activity is suggested (Rao et al., 1982). Similarly, Parodi et al. (1981) reported MDA to have dose-related mutagenic activity in TA100 with an activation system, but no significant increase in histidine revertants was reported in TA98 under the same conditions (plate incorporation, 6.25-50 μ g MDA/plate). In an abstract, Takemura and Shimizu (1978) reported that MDA was mutagenic to TA100 but not TA98 when tested with an activation system.

Chromatid aberrations and sister chromatid exchange in human leukocytes were not induced in vitro by unspecified concentrations of MDA with or without metabolic activation by rat-liver microsomal enzymes (Ho et al., 1978). Parodi et al. (1981) reported that MDA produced significant ($P < 0.002$) DNA-fragmentation (determined by DNA elution rate) in hepatocytes from rats treated with a single intraperitoneal dose of 0.37 mmole MDA/kg.

5.3. TERATOGENICITY

Pertinent data regarding the teratogenic effects of MDA in mammals were not located in the available literature.

5.4. OTHER REPRODUCTIVE EFFECTS

Pertinent data regarding the effects of MDA on other reproductive parameters were not located in the available literature.

5.5. CHRONIC EFFECTS

Groups of rats were treated with dietary MDA at 1000 ppm for 8, 16, 24, 32 or 40 weeks. Of the rats treated for 32 or 40 weeks, bw gain was reduced and liver-to-body weight ratio was elevated (Fukushima et al., 1979). Chronic MDA treatment resulted in fibrotic changes of the liver, bile duct proliferation, and oval-cell infiltration into the hepatic portal areas. These changes became apparent after 8 weeks of treatment and the severity of the changes increased with length of treatment.

During 13-week studies in which F344 rats and B6C3F1 mice of both sexes were exposed to MDA-2HCl in the drinking water, bile duct hyperplasia and depressed bw were prevalent signs of toxicity (NTP, 1983). Bile duct hyperplasia was reported in all male (10/10) and female (10/10) rats receiving 800 mg MDA/l and in 4/10 males and 3/10 females receiving 400 mg MDA/l. Controls had no bile duct hyperplasia. Body weight was depressed 26 and 21% in female and male rats, respectively, after treatment at 800 mg MDA/l. In mice, 5/10 males and 4/10 females treated at 400 mg MDA/l developed moderately severe bile duct hyperplasia, while controls had none (0/10). Male and female mice treated at 400 mg MDA/l had 13% and 7% decreased bw, respectively (NTP, 1983).

Two-year carcinogenesis studies were conducted in which rats and mice of both sexes were exposed to MDA-2HCl at levels of 150 and 300 mg MDA/l drinking water (NTP, 1983). These studies provide information on systemic toxicity as well as carcinogenicity. Experimental details, and effects on bw and survival were described in Section 5.1. Following histopathological

examination, increased incidences of nonneoplastic lesions of the thyroid (hyperplasia and cysts) were identified in high-dose female rats (19/48 vs. 6/49). Increases in liver lesions, including fatty metamorphosis and focal cellular changes, were reported in male and female rats. Fatty metamorphosis occurred in 28/50 low-dose and 33/50 high-dose males (14/50 controls) and focal cellular changes occurred in 38/50 low-dose and 36/50 high-dose males (14/50 controls). In females, the incidences of fatty metamorphosis (20/50 low-dose; 11/50 high-dose; 7/50 controls) and focal cellular change (17/50, 10/50 and 5/50) were only slightly elevated (NTP, 1983). Mineralization within the kidney was noted in high-dose male rats (19/50 vs. 9/50 in controls).

In mice, nonneoplastic lesions of the thyroid were markedly more prevalent in both sexes treated with 300 mg MDA/l (20/49 and 0/47 in treated and control males; 23/50 and 1/50 in treated and control females). Degeneration of the renal cortical tubules increased in a dose-related fashion in male and female mice (18/49, 34/50, 36/50 in control, low- and high-dose males; 6/50, 21/50, 35/50 in females). Mineralization of the renal papilla also showed a dose-related increase in mice of both sexes (1/49, 2/50, 12/50 in control, low- and high-dose males; 1/50, 1/50, 14/50 in females) (NTP, 1983).

A long-term oral study has been performed on dogs by Deichmann et al. (1978). MDA, administered to female beagles 3 days/week at doses of 70 mg/day for ~4-7 years produced moderate to severe gross and histopathological changes in their livers and less severe changes in their kidneys or spleens. Purified MDA was administered to 5 dogs and crude MDA was administered to 4 dogs; the chemicals were dissolved in corn oil and administered

in gelatin capsules. No concurrent controls were included in the experiment. In dogs treated with either purified or crude MDA, histopathologic changes in the livers ranged from swelling of hepatic cells, some disruption of the lobular patterns, and fatty infiltration to hepatocellular degeneration, distortion of the lobular pattern, central zonal fatty degeneration with necrosis, and distention of the bile ducts. Two dogs (one from each group) died of conditions related to hepatic damage. Four dogs (two from each group) had histopathological changes in their kidneys, such as glomerulonephritis. Three dogs (two that received purified MDA and one that received crude MDA) had histopathological changes in their spleens: hemosiderosis, splenitis or hemorrhagic congestion. The primary purpose of this study had been to investigate the carcinogenicity of purified and crude MDA to the urinary bladder, but no neoplastic changes were seen in this organ; one dog treated with purified MDA had foci of mucosal hyperplasia in the bladder.

5.6. OTHER RELEVANT INFORMATION

Acute exposure to MDA in humans causes hepatotoxic symptoms and jaundice (bilirubin levels as high as 29.3 mg/100 ml) (Kopelman et al., 1966a). Of eight liver biopsies taken from 7 patients exposed to MDA-contaminated bread 6 biopsies were taken during acute stages of toxicity and 2 were conducted after apparent recovery to identify residual hepatic damage (Kopelman et al., 1966b). Initially, hepatic damage included portal cellular infiltration, cholestasis and increased liver-cell mitoses. Biopsies taken several weeks after the onset of symptoms showed slight hepatic scarring, but suggested recovery of normal hepatic function (Kopelman et al., 1966b).

Workers exposed to MDA used as an epoxy resin developed symptoms of jaundice, weakness and abdominal pain similar to those reported in persons

who ate contaminated bread (McGill and Motto, 1974). Absorption of MDA was concluded to be predominantly through the skin of cloth-gloved hands, although other percutaneous or inhalation absorption could not be ruled out. Levels of MDA in the air, before precautionary measures, were 0.1 ppm, while workers were dermally exposed to pure powdered MDA during the blending of the epoxy resin. In all, 13 of 100 employees working with MDA developed jaundice and hepatic toxicity, each becoming ill within 1-18 days of working with MDA.

Hepatotoxicity similar to that seen in human cases has been reported in rats treated with MDA (Gohlke and Schmidt, 1974). Oral doses of 8 and 50 mg/kg were reported to be the morphological threshold and most effective dose, respectively. Toxic symptoms included hepatomegaly, fatty degeneration, cholangitis, increased mitotic activity and "paraportal" parenchymal necrosis. MDA treatment decreased the activity of some hepatic enzymes, including succinic dehydrogenase, lactate dehydrogenase and acid phosphatase, and increased the activity of glucose-6-phosphate dehydrogenase and alkaline phosphatase (Gohlke and Schmidt, 1974). Schmidt et al. (1981) reported changes in hepatic lipid metabolism and glycogen content in rats treated orally with MDA. Sell (1983) reported that the livers of rats treated with dietary MDA (0.15% of the diet) for up to 12 weeks reorganized so that at 12 weeks of treatment, about one-third of the lobule was occupied by ducts and dense connective tissue, and cellularity was decreased. Hepatic changes seen at 1 week of treatment included periportal edema, infiltration of mononuclear and polymorphonuclear cells, and disruption of the structure of the bile ducts including signs of cell damage (cytoplasmic vacuolization and pyknosis).

6. AQUATIC TOXICITY

Pertinent data regarding the effects of MDA on aquatic organisms or the aquatic environment were not located in the available literature.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

The American Conference of Governmental Industrial Hygienists (ACGIH, 1980, 1982) TLV for MDA is 0.1 ppm (0.8 mg/m³) for dermal and inhalation exposure. The recommended STEL is 0.5 ppm (4.0 mg/m³).

7.2. AQUATIC

Guidelines and standards for the protection of aquatic organisms from the toxic effects of MDA were not located in the available literature.

8. RISK ASSESSMENT

The carcinogenic potential of MDA has been studied in rats and mice following administration by gavage (Munn, 1967), diet (Yoshimura, 1981), drinking water (NTP, 1983) and subcutaneous injection (Steinhoff and Grundmann, 1970). Two studies reported by Munn (1967) in which rats received total doses of 3.3 and 6 g/kg of MDA by gavage during 121 days and ~18 months, respectively, showed no statistically verifiable evidence of carcinogenicity.. MDA administered at 1000 ppm in the diet for up to 40 weeks was not carcinogenic to male rats (Yoshimura, 1981). No other details were available for this Japanese study. Subcutaneous administration of MDA produced cancers in 50% of the treated rats, but 26% of the vehicle controls also developed cancer, making a valid conclusion difficult (Steinhoff and Grundmann, 1970). The NTP (1983) bioassay of MDA-2HCl, administered in drinking water, reported statistically significant increases in the incidence of several tumor types in both male and female rats and mice of the strains tested. Significant increases in thyroid follicular-cell carcinoma were reported in male rats treated at 300 mg MDA/l, while thyroid follicular-cell adenoma was elevated in female rats and both sexes of mice treated at this dose. Female rats treated at 300 mg MDA/l also had an increased incidence of thyroid C-cell adenoma. Neoplastic nodules of the liver were increased in both dose groups of male rats and all dose and sex groups of mice had increased incidences of hepatocellular carcinoma/adenoma. Male mice treated at both dose levels had increased adrenal pheochromocytomas, and malignant lymphoma among both dose groups of female mice was significantly elevated.

The data from the chronic study with rats and mice exposed to MDA-2HCl in the drinking water (NTP, 1983) can be used to estimate a carcinogenic potency factor for humans.

From the data on hepatocellular tumors (adenomas or carcinomas), a range of risk estimate values can be obtained. While the data from male rats (1, 12 and 25 hepatic neoplastic nodules per 50 animals for control, low-dose, and high-dose groups, respectively) and female mice (4, 15 and 23 hepatocellular tumors per 50 animals controls, low-dose and high-dose groups, respectively) suggest a dose-response relationship, the data from the male mice (17/49 controls, 43/50 low-dose and 37/50 high-dose) preclude a definitive statement of such a relationship. The average daily doses, based upon water consumption and mean body weight data for animals exposed to 150 and 300 mg MDA/l, were reported to be 9.0 and 16.0 mg MDA/kg bw/day, respectively for male rats; 25 and 57 mg MDA/kg bw/day, respectively, for male mice; and 19 and 43 mg MDA/kg bw/day, respectively, for female mice (NTP, 1983). Based upon the development of hepatic neoplastic nodules, and using the linearized multistage model developed by Kenneth Crump and adopted by the U.S. EPA (1980), human q_1^* values of 2.2×10^{-2} and 2.5×10^{-2} (mg/kg/day) $^{-1}$ can be derived for MDA from female mice and male rat data, respectively. The corresponding doses associated with an increased lifetime cancer risk of 10^{-5} accordingly are 4.6×10^{-3} mg/kg/day (3.2×10^{-3} mg/day for a 70 kg man) and 4.0×10^{-3} (2.8×10^{-3} mg/day for a 70 kg man), respectively. Based upon the quality of the data, the human q_1^* of 2.5×10^{-2} and its associated lifetime increased cancer risk level of 4.0×10^{-5} are considered more appropriate for estimation of human cancer risk due to exposure to benzenamine, 4,4'-methylenedibis. It should be noted that although there was a statistically significant increase in liver tumors in both the high- and low-dose groups of male mice when compared to controls, high mortality in the high-dose group precludes derivation of a meaningful carcinogenicity potency factor. Complete data for derivation of the q_1^* are presented in Appendices B through D.

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APPENDIX A
LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of:

CA SEARCH (Files 308, 309, 310, 311, 320)
TOXLINE
MEDLINE
RTECS
SCI SEARCH
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
EPCASR
Chemical Industry Notes

These searches were conducted in June, 1983. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7th), and the following secondary sources were reviewed:

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APPENDIX B
Cancer Data Sheet for Derivation of q_1^*
Using Male Rat Data

Compound:	MDA-2HC1
Reference:	NTP, 1983
Species, Strain, Sex:	Rats, F344, male
Body Weight:	0.416 kg, low dose; 0.414 kg, high dose, measured
Length of Exposure (l_e)	= 721 days
Length of Experiment (L_e)	= 735 days
Lifespan of Animal (L)	= 735 days
Tumor Site and Type:	liver; neoplastic nodule
Route, Vehicle:	oral; drinking water

Experimental Doses or Exposures to MDA-2HC1	Transformed Dose (mg/kg/day) of MDA*	Incidence No. Responding/ No. Tested (or Examined)
0	0	1/50
150 mg MDA/l	9	12/50
300 mg MDA/l	16	25/50

*Reported by NTP (1983) based on mean daily water consumption and body weight.

Human $q_1^* = 2.493 \times 10^{-1} \text{ (mg/kg/day)}^{-1}$

10^{-5} risk level = $4.01 \times 10^{-5} \text{ mg/kg/day} = 2.81 \times 10^{-3} \text{ mg/day}$ of MDA for 70 kg man

APPENDIX C
Cancer Data Sheet for Derivation of q_1^*
Using Male Mouse Data

Compound:	MDA-2HC1
Reference:	NTP, 1983
Species, Strain, Sex:	Mice, B6C3F ₁ , male
Body Weight:	0.040 kg, low dose; 0.037 kg, high dose, measured
Length of Exposure (l_e)	= 721 days
Length of Experiment (L_e)	= 735 days
Lifespan of Animal (L)	= 735 days
Tumor Site and Type:	liver; neoplastic nodule (adenoma or carcinoma)
Route, Vehicle:	oral; drinking water

Experimental Doses or Exposures to MDA-2HC1	Transformed Dose (mg/kg/day) of MDA*	Incidence No. Responding/ No. Tested (or Examined)
0	0	17/49
150 mg MDA/l	25	43/50
300 mg MDA/l	57	37/50

*Reported by NTP (1983) based on mean daily water consumption and body weight.

Human $q_1^* = 3.989 \times 10^{-1} \text{ (mg/kg/day)}^{-1}$

10^{-5} risk level = $2.57 \times 10^{-5} \text{ mg/kg/day} = 1.80 \times 10^{-3} \text{ mg/day}$ of MDA for 70 kg man

APPENDIX D
Cancer Data Sheet for Derivation of q_1^*
Using Female Mouse Data

Compound:	MDA-2HC1
Reference:	NTP, 1983
Species, Strain, Sex:	Mice, B6C3F ₁ , female
Body Weight:	0.038 kg, low dose; 0.037 kg, high dose, measured
Length of Exposure (t_e)	= 721 days
Length of Experiment (L_e)	= 735 days
Lifespan of Animal (L)	= 735 days
Tumor Site and Type:	liver; neoplastic nodule (adenoma or carcinoma)
Route, Vehicle:	oral; drinking water

Experimental Doses or Exposures to MDA-2HC1	Transformed Dose (mg/kg/day) of MDA*	Incidence No. Responding/ No. Tested (or Examined)
0	0	4/50
150 mg MDA/d	19	15/50
300 mg MDA/d	43	73/50

*Reported by NTP (1983) based on mean daily water consumption and body weight.

Human $q_1^* = 2.207 \times 10^{-1} \text{ (mg/kg/day)}^{-1}$

10^{-5} risk level = $4.57 \times 10^{-5} \text{ mg/kg/day} = 3.20 \times 10^{-3} \text{ mg/day}$ of MDA for 70 kg man